Drug Metabolism

Metabolism [Biotransformation]:

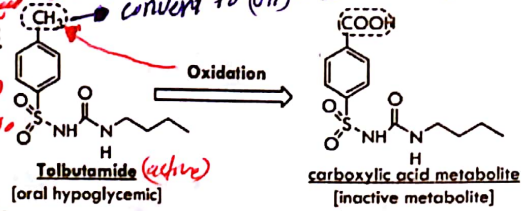
- Xenobiotics are excreted either unchanged or after biotransformation.
  [**Xenobiotics**: drug & foreign compounds to body]
- **Drug metabolism**: A process, by which drugs are rendered more water soluble, less reabsorbed → **more excreted** → **Detoxification**.

most common active to inactive

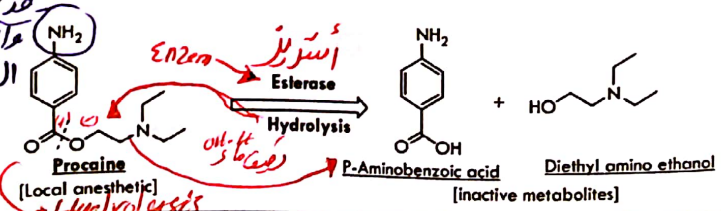
But metabolism may cause other effects:

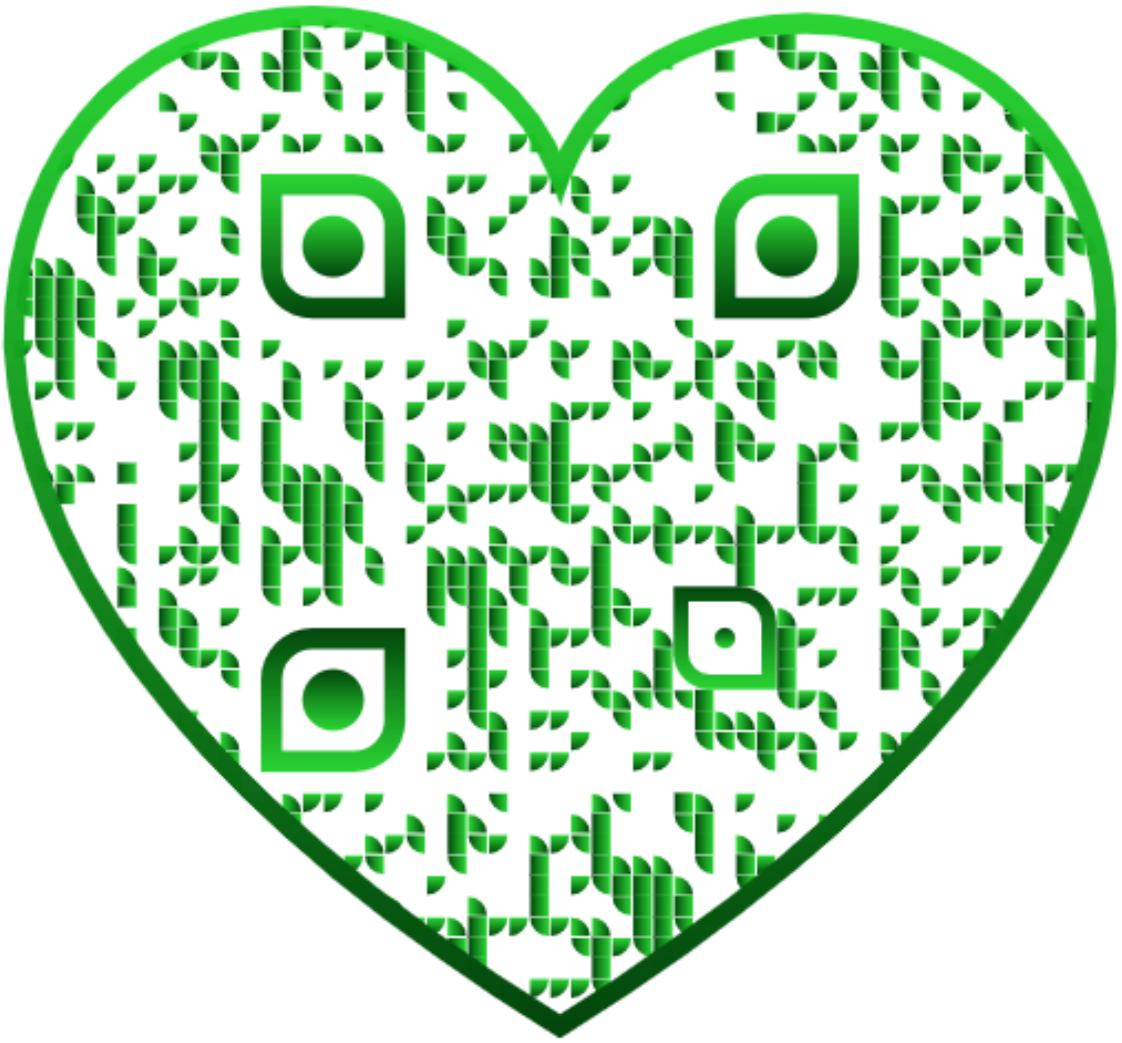
1.Formation of inactive or less active metabolite from active drug: [MOST COMMON]

Example 1:

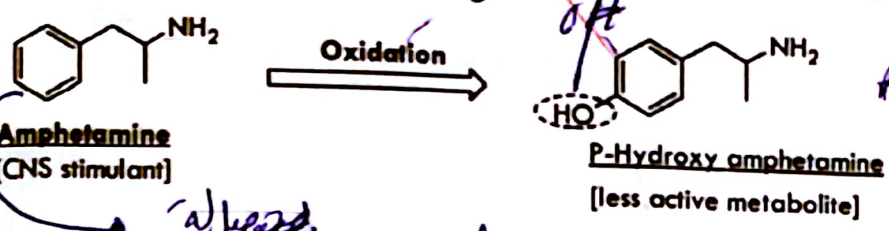


Example 2:





Example 3:



phase 1

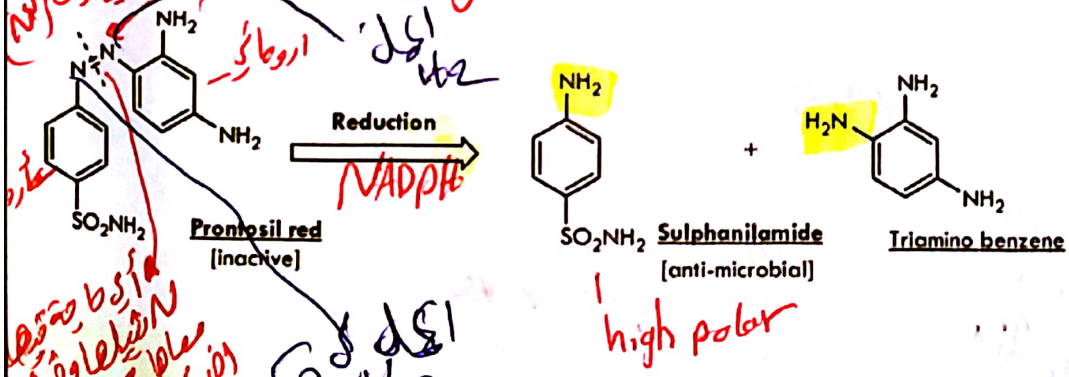
epoxid → phenol

method → oxidation

Enzyme → cytochrom P-450

2. Formation of active metabolite from initially inactive drug [Prodrugs]:

Example 1:



method → Reduction

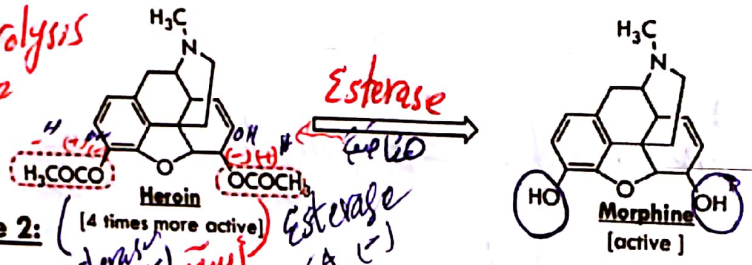
Enzyme → NADPH

high polar

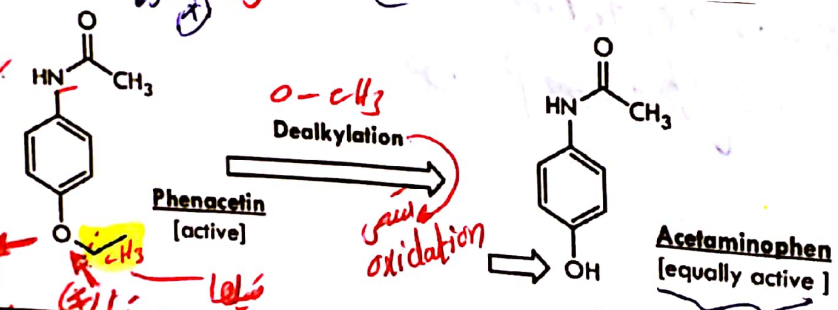
3. Formation of active metabolite from initially active drug [Co-activation]:

Enzymatic biotransformation doesn't always terminate its action.

Example 1:

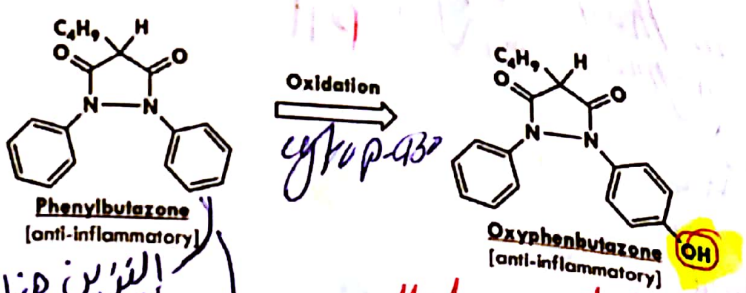


Example 2:



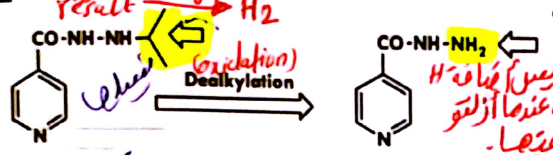
3. Formation of active metabolite from initially active drug [Co-activation]:

Example 3:



4. Formation of active metabolite having a pharmacological action different from parent drug:

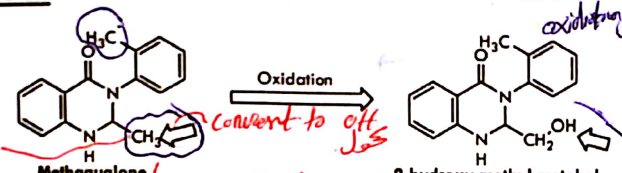
Example 1:



Iproniazide
[anti-depressant]

Isoniazide
[anti-T.B.]

Example 2:

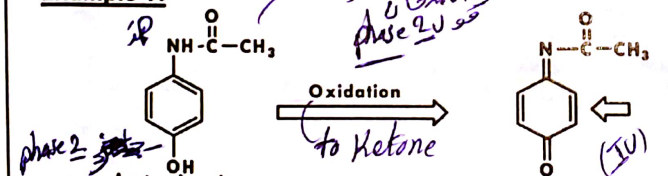


Methaqualone
[sedative-hypnotic]

2-hydroxy methyl metabol
[hypolipidemic]

5. Formation of toxic metabolite from initially less toxic drug

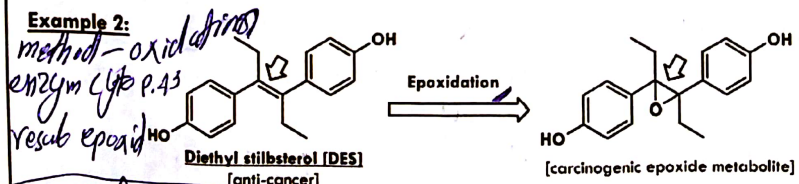
Example 1:



Acetaminophen
[antipyretic-analgesic]

N-acetylimido quinone
[toxic metabolite]

Example 2:



Diethyl stilbsterol [DES]
[anti-cancer]

[carcinogenic epoxide metabolite]

unchanged → highly polar

Sites of drug metabolism:

① In liver [Hepatic]	② Extra-Hepatic
① **The main site of metabolism** as it's full of **metabolizing enzymes**. • **1st Pass Effect:** Orally administered drugs [most of drugs] → pass through the liver before being absorbed & reaching the systemic circulation. 	• As intestinal mucosa, kidney, lung. • **Intestinal bacterial flora** in the intestine play role in drug metabolism : 1. **Catalyze hydrolysis of conjugated compounds eliminated in bile**. E.g. bacterial sulfatases hydrolyzed sulfate conjugation of **Premarin** [oral estrogen] giving free estrogen which reabsorbed from intestine into portal circulation. 2. **Reduction of nitro group in nitroimidazole & azo group of azides**. E.g. **Sulfasalazine** [anti-infective & anti-inflammatory used in ulcerative colitis] → reduced by bacteria in colon → 5-amino salicylic acid + sulphapyridine.

unchanged mean → polar

From less polar to high polar

Metabolism

Phase I [Functionalization Reactions]

•**The purpose of Phase I is to make drug more polar → readily excreted**

➢ **It's performed to:**

1. **Introduce new functional gp** [e.g. aromatic &aliphatic hydrolxylation].
2. **Modify existing functional gp** [e.g. rduction of ketones & aldehydes to alcohols / oxidation of alcohols to acids / hydrolysis of esters to acids]
3. **Expose a functional gp [Acceptor site] for phase II**

Phase II [Conjugation Reactions]

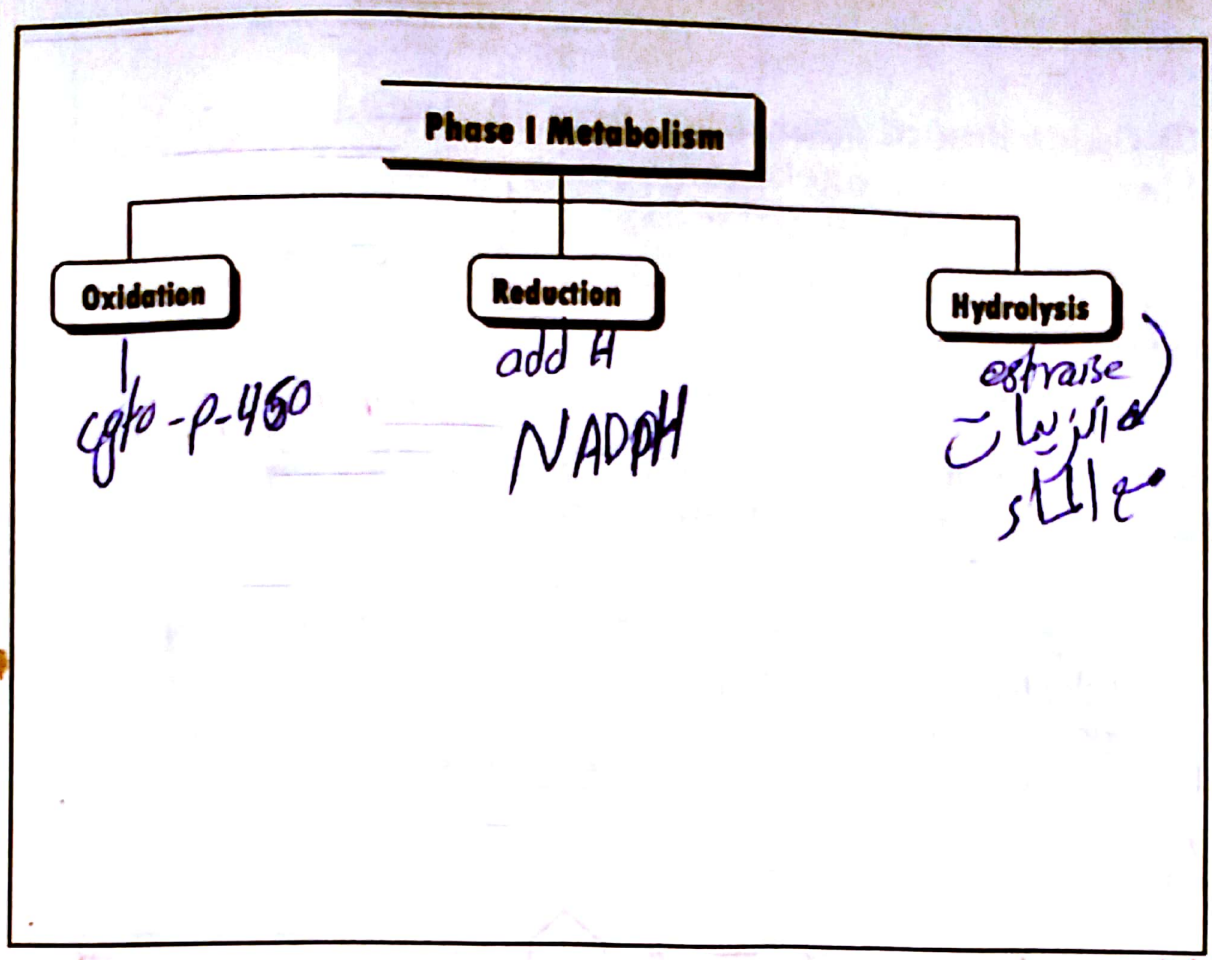
They are enzymatic reactions where **functional groups as OH, NH_2 groups are masked by addition of new polar endogenous group → ↑ solubility & excretion.**

Most of drug undergo both phase1 and 2

N.B:

•**Xenobiotics that are resistant to metabolizing enzymes are already hydrophilic → excreted unchanged.** highly polar

•**Some drugs may pass directly into phase II.**



transfer O2 from liver to drug

B6 — NADPH

[I] OXIDATION REACTIONS

- The **most common** reaction for drug metabolism.
- Catalyzed by group of **membrane-bound mono-oxygenase enzymes** found in cytoplasmic reticulum of **liver & other extra-hepatic tissues**.
- These mono-oxygenases are called: **Cytochrome P-450 mono-oxygenase enzyme system [CYP-450]** or **Mixed Function Oxidases [MFO]** are able to add polar groups to a wide varity of drugs
- They are made of several components:
  - **Cytochrome P-450:** heme protein responsible for transferring an oxygen atom to the substrate RH. [This reaction needs NADPH as reducing agent].

$$RH + O_2 + NADPH + H^+ \xrightarrow{\text{Cytochrome P-450}} R\text{-}OH + H_2O + NADP^+$$

oxidation - Reduction → Reaction

- **1.NADPH-dependent cytochrome P-450 reductase.**
- **2.NADH-linked cytochrome b_5.**

With cofactors NADPH & NADH → **supply electrons** "reducing equivalents" needed in overall oxidation reactions.

① Oxidation of Aromatic rings [Arenes]
[Aromatic Hydroxylation

- **The major route of drugs having Benzene rings [aromatic compounds = arenes].**

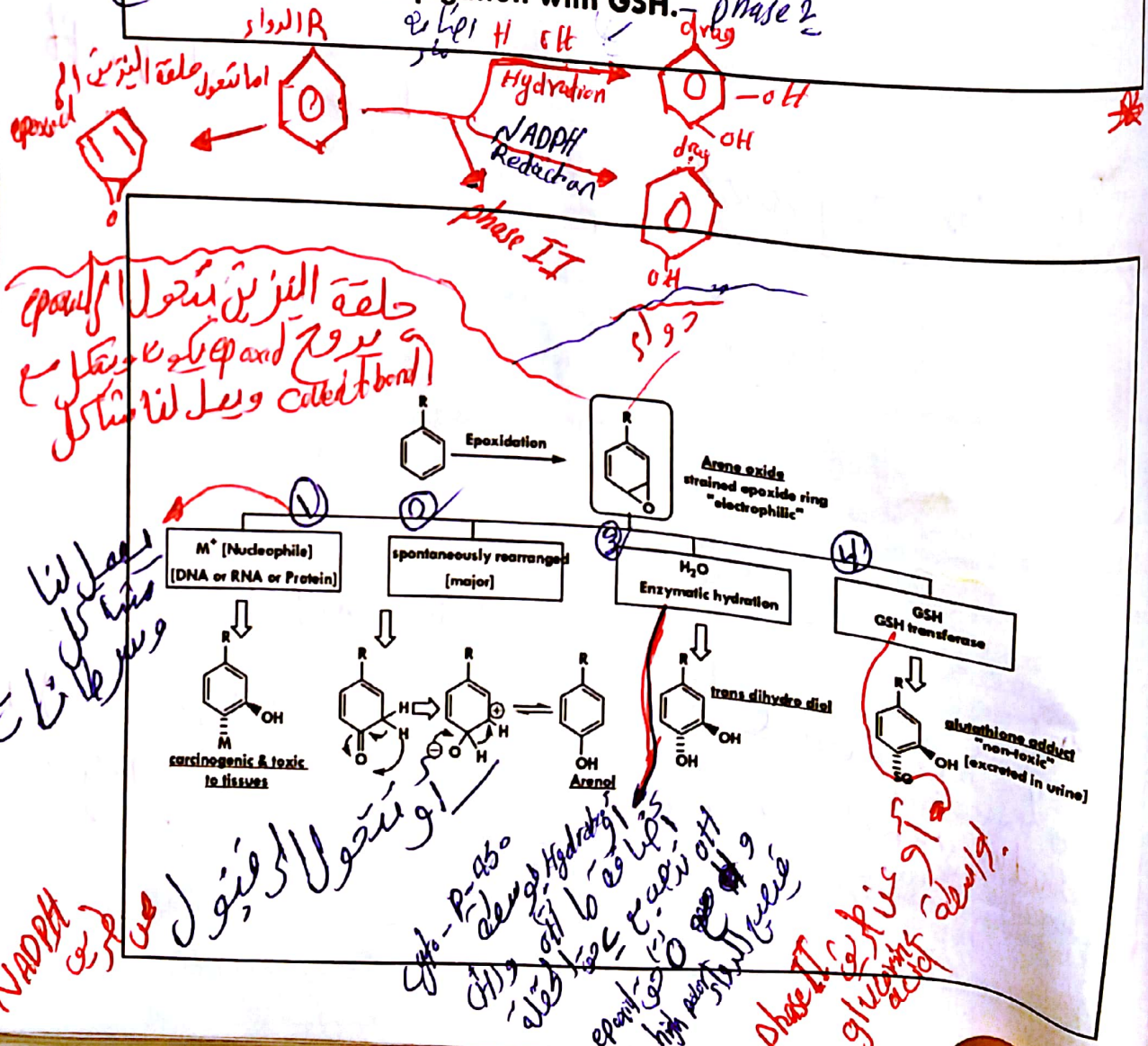
- **Phenolic metabolites [Arenols]** are produced.

- **It's done through formation of epoxide intermediate [Arene oxide] → rearrange spontaneously to phenolic product.**

- The **arene oxide** is **highly toxic** due to its **electrophilic** characters → **bind to any nucleophile** in the body [DNA, RNA or Protein] → **cellular damage**.

- **Detoxification** is done through:

1. [i] Spontaneous rearrangement to phenols [major]
2. [ii] Enzymatic hydration to trans-dihydrodiols.
3. [iii] Enzymatic conjugation with GSH.

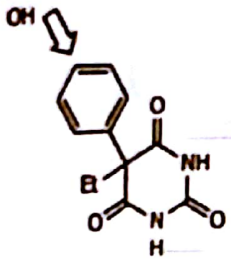


① إذا معك حلقة بترين يحدث الاستبدال في para

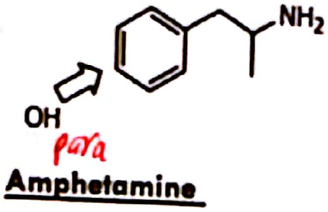
إذا فيه زحمة في para يرجع ortho

Rules of Aromatic Hydroxlyation:

1. If mono-substituted aromatic ring → Para-Hydroxylation usually predominate > ortho.



Phenobarbital



Amphetamine

ملاحظة

إذا الدواء معندوش S, O, N جاهزة لايكن يدخل phase I

لازم مثلا يكون عندك NH او OH جاهزة

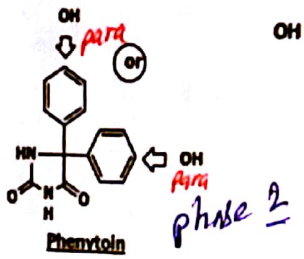
وتذكر عندما كتبت أطول لك ضيف O وH وريل H

على شان أجهز الدواء لـ phase 2

② إذا معك حلقتين أبدأ بالحلقة الأولى إذا متفعشن أفضل للحلقة الثانية

إذا متفعشن يروح phase II

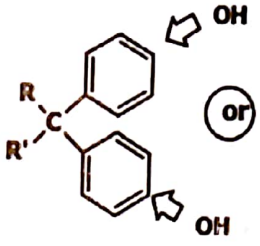
2. If the compound with two identical aromatic rings → oxidation of one ring only.



Phenytoin

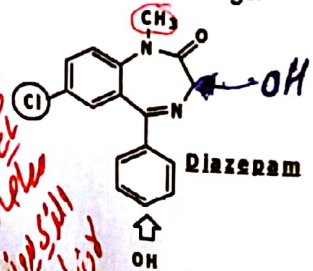
phase 2

Phenyl butazone

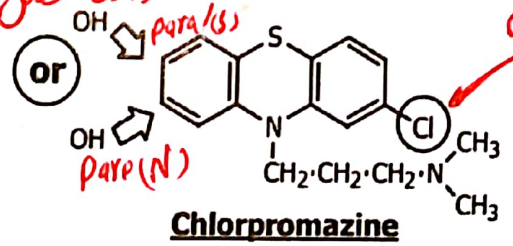


③ Hydroxylation is more rapidly in electron-rich rings [with electron-donating group] → activated rings.

حلقة يدون أفضل حيث يحط OH



Diazepam

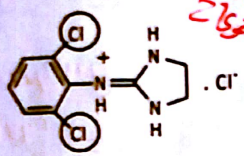


Chlorpromazine

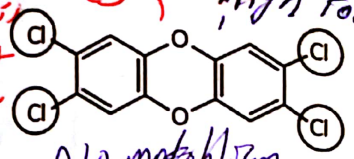
تنشيط

إذا معك حلقتين أفضل حلقة فيها S, N أو فيها S, N أفضل حلقة

4.Deactivated aromatic rings [with electron-withdrawing group as Cl, NO2, COOH...] → hydroxylated or slowly hydroxylated.



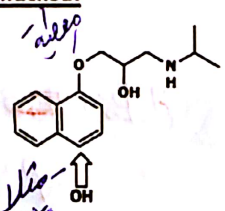
Clonidine HCl



high toxic

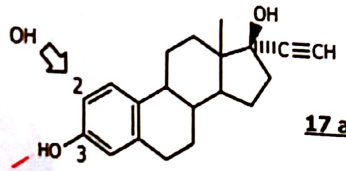
No metabolism
difficult to metabolize

5.If the drug with two aromatic rings → hydroxylation occurs in the more electron-rich ring & usually one ring is attacked.



Propranolol

6.Hydroxylation occurs at ortho position if para position is occupied.

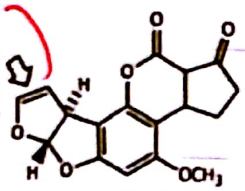


17 alpha-ethinyl estradiol

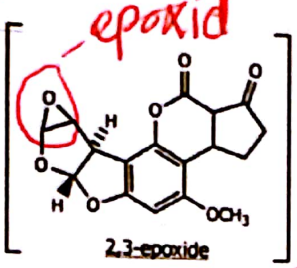
بعض الفطريات تنتج مواد Aflatoxin سموم / مواد مسرطنة

② Oxidation of Olefins

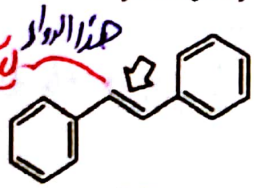
• Some epoxides are **toxic** → extremely **reactive** & bind easily to proteins, DNA & RNA. For E.g. **Aflatoxin B_1** [carcinogenic agent formed by *Asperigillus flavus* growing on pea nut] & **Stilbene, Diethyl stilbsterol**.



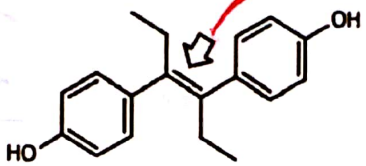
Aflatoxin B_1
[carcinogenic]



2,3-epoxide



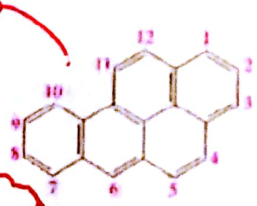
Stilbene



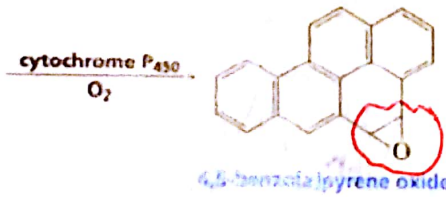
Diethyl Stilbsterol [DES]

Trat Brest cancer

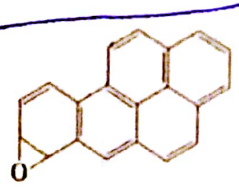
مهم/ الأدوية التي فيها double bond تتحول الى epoxid في الكبد
لذلك يجب عمل فحوص للكبد عند استعمال الأدوية التي فيها double bond

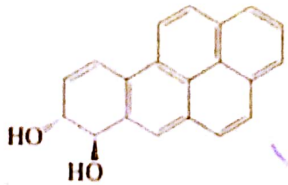


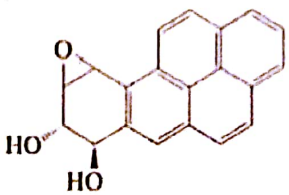
benzo[a]pyrene



4,5-benzo[a]pyrene oxide



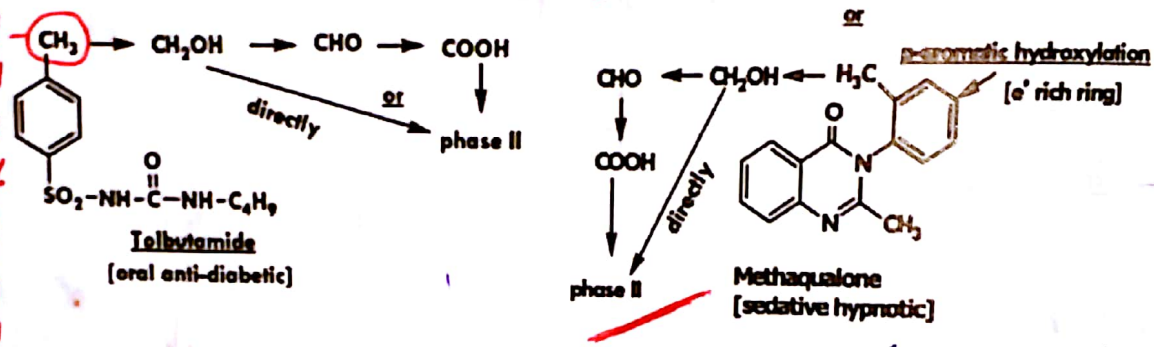




a diol epoxide

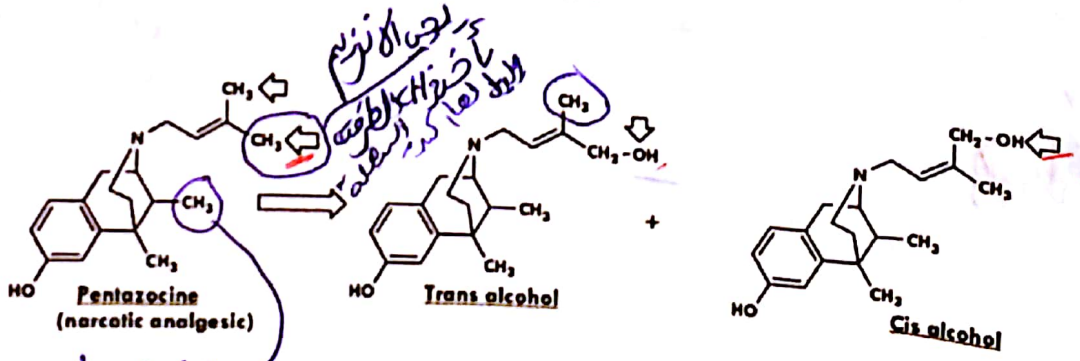
③ Oxidation at Benzylic carbon

- **Benzylic carbon** is C attached to aromatic ring.
- By oxidation → **alcohol [carbinols].**
- **1ry alcohol** → aldehyde → carboxylic acid **While 2ry alcohol** → ketone.
- **Alcohols** may **directly go to phase II** & conjugated with glucuronic acid.



وجود CH_3 يسهل من خروج الدواء.

④ Oxidation at Allylic carbon

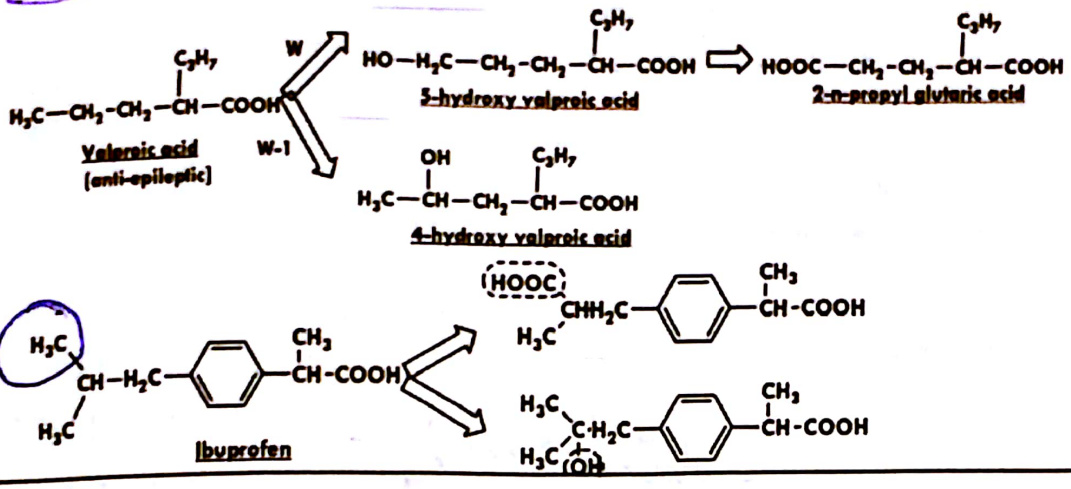


oxidation
Cyto-P-450

⑤ Oxidation of aliphatic carbons

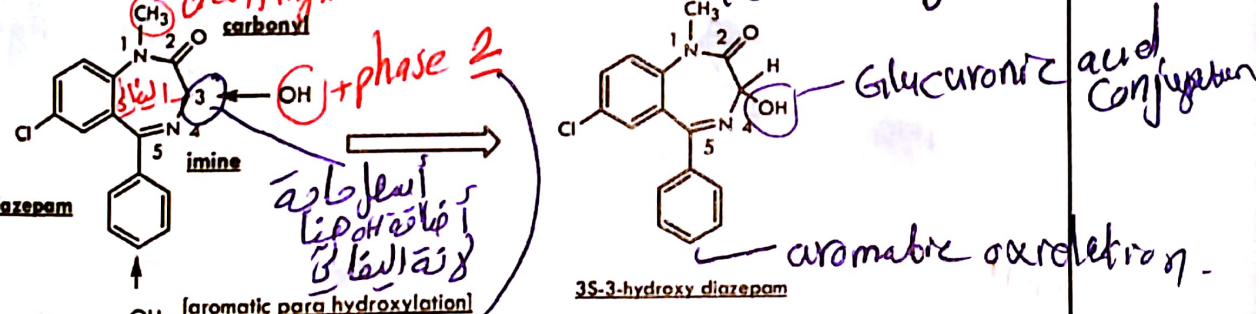
Aliphatic Carbons:

- This oxidation commonly takes place in drug molecules with straight or branched alkyl chains.
- Alcohol metabolites formed → further oxidation to aldehydes & ketones. [Or directly conjugated with glucuronic acid].



⑥ Oxidation of C atom α to carbonyl & imine

→ Give The metabolism ?



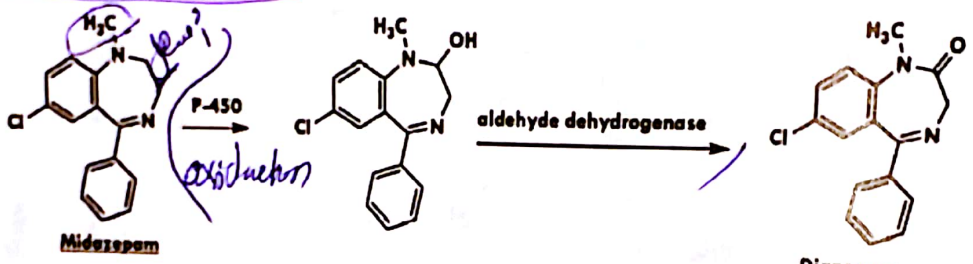
N-dealkylation

Glucuronic acid Conjugation

aromatic oxidation.

⑦ Oxidation of alcohols & aldehydes

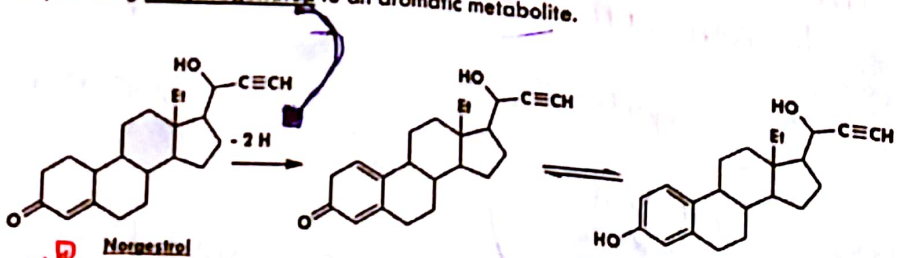
- Benzylic, allylic, aliphatic hydroxylation → alcohols [or carbinols intermediates].
- Alcohols formed → **direct conjugation** OR **further oxidized** to aldehydes [1ry alc.] or ketone [2ry alc.]
- **Aldehydes** comes from **alcohols** or **from oxidative deamination** [or 1ry amines] → **oxidation to carboxylic acid** derivative.
- 2ry alcohol → oxidation to ketone. This reaction may be reversed readily by alcohol dehydrogenase enzyme **[2ry alcohol are more polar, so more likely to be conjugated than ketone]**



Midazepam — Diazepam

⑧ Oxidative aromatization

- Alicyclic drug **dehydrogenated** to an aromatic metabolite.



Norgestrel — 17-alpha-ethinyl-1,3,5(10)-estratriene-3,17-beta-diol

dealkylation

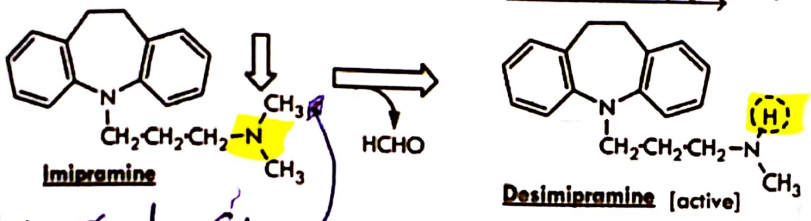
Oxidation of Heteroatom-containing compounds

- [i] Hydroxylation of C directly attached to heteroatom [N,S or O] [to it]
- [ii] Direct attack on the hetero atom [N or S but not O]

(1) Oxidation of C-N systems

•The α-carbon oxidation is catalysed by cytochrome P-450 enzyme system. **There must be one H atom at least on this carbon.**

3° amine –R [Rapidly] → 2° amine –R [slowly] → 1° amine



Imipramine — Desimipramine [active]

أي حاجة جانب الـ N
بتطلع وتعيش H
dealkylation

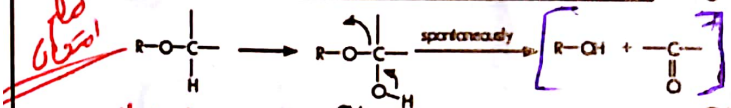
(2) C - O system

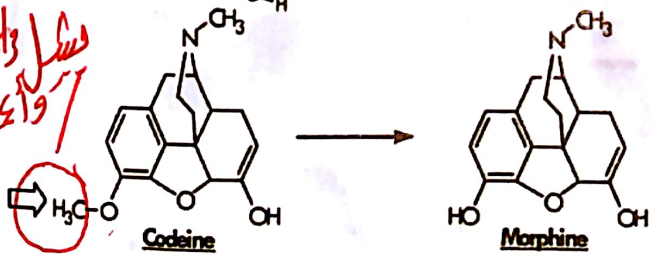
•Involves **O-dealkylation** & occurs mainly in ethers.

•Done by *hydroxylation of C α to O* → *spontaneous cleavage* of C-O bond → *phenol or alcohol.*

demethylation

•**Small alkyl gps rapidly O-dealkylated**. E.g. **Codeine.**

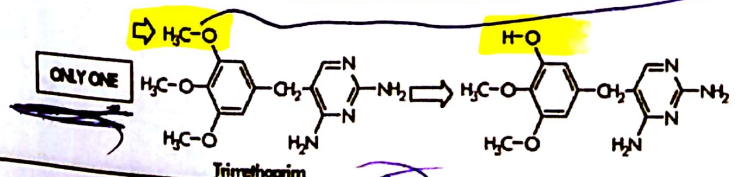




Codeine — Morphine

methyl → dealkylation (oxid)
Enzyme → cyto P-450
Results → morphine

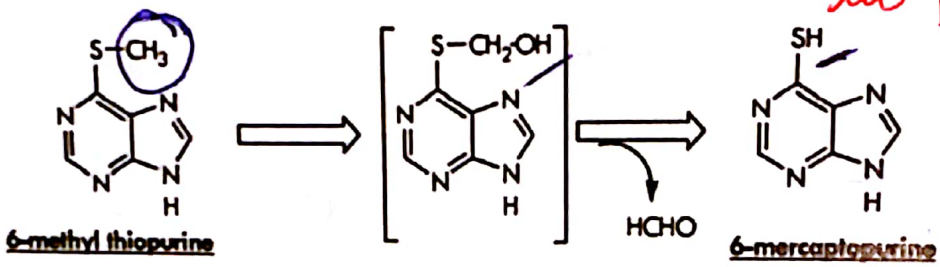
•If **several non-equivalent methoxy** groups → selective dealkylation of **only one** methoxy. E.g. **Trimethoprim.**



Trimethoprim

C - S systems

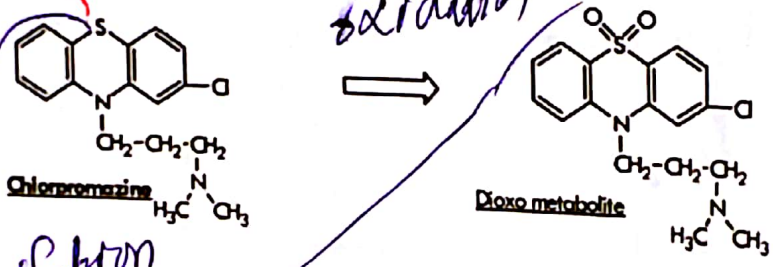
1. S-dealkylation:



6-methyl thiopurine — 6-mercaptopurine

2. S-oxidation:

•Give sulfoxide [S=O] → or further oxidation gives sulfone [O=S=O]



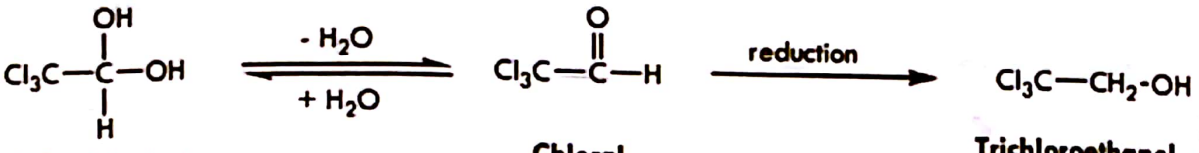
Chlorpromazine — Dioxo metabolite

[II] REDUCTION REACTIONS

[II] REDUCTION REACTIONS

[i] Reduction of Aldehydes & Ketones:

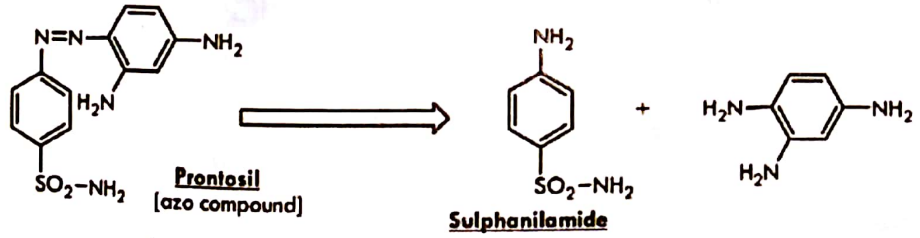
- Reduction of **aldehyde** → **1ry alcohol** [of **ketone** → **2ry alcohol**].
- Majority of aldehydes oxidized to carboxylic acids but may reduced to alcohols especially if attached to **e-withdrawing group**. [c.f. oxidation] Exmple:



Chloral hydrate — **Chloral** — **Trichloroethanol** [active]

[ii] Reduction of Azo & Nitro compounds [to 1ry NH_2]:

- Leads to formation of **1ry amines**.



Prontosil [azo compound] — **Sulphanilamide**

أغلب الأدوية تكون على شكل أستر لأن إنزيم الإستريز موجود بكميات كبيرة في أجسامنا

Phase I Metabolism

Oxidation | Reduction | Hydrolysis

[III] HYDROLYTIC REACTIONS

[i] Ester Hydrolysis | [ii] Amide Hydrolysis

إذا أريد دواء يدخل بسرعة أحط CH_3 أحط استر.

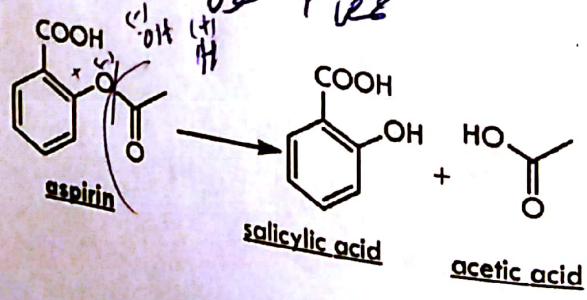
Long duration

إذا اريد أخلي الدواء أكبر الـ chain أضيف مجموعات ماصة أحول الإستر الى أميد

الناتج في الأميد ضعف الطاقة يحتاج طاقة يعمل بسرعة

[i] Ester Hydrolysis:

- Catalyzed by **Esterases** which are non-specific & widely distributed in liver, kidney, intestine.
- Major pathway for esters → facile hydrolysis.
- Hydrolytic products are **alcohol & acid** → contain functional groups that can be conjugated.



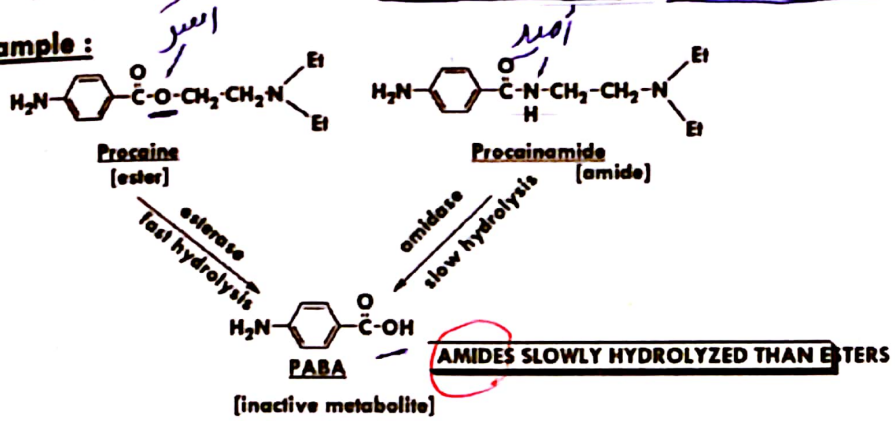
[ii] Amide Hydrolysis:

- Catalyzed by **microsomal amidases.**
- Hydrolytic products are → **carboxylic acid & amine metabolites.**

- Catalyzed by **microsomal amidases.**
- Hydrolytic products are → **carboxylic acid & amine metabolites.**

Ester hydrolysis is easy to occur → rapidly hydrolyzed > amide hydrolysis.

Example :



الخلاصة

Reaction	Chemical modification	Examples (substrates)
Oxidations		
Oxidation of alcohols and aldehydes	$R-CH_2OH \rightarrow R-C(=O)H \rightarrow R-COOH$	Benzyl aclohol Pyridoxine
Oxidation of aliphatic chains	$R-CH_2-CH_3 \rightarrow R-CH(OH)-CH_3$ und $R-CH_2-COOH$	Barbiturates
Oxidative N-dealkylation	$R^1-N(H)-CH_2R^2 \rightarrow R^1-NH_2 + R^2-C(=O)H$	Ephedrin Lidocaine Methamphetamine
Oxidative deamination	$R-CH_2-NH_2 \rightarrow R-C(=O)H + NH_3$	Fomocaine Histamine Mescalin Noradrenaline
Oxidative O-dealkylation	$R^1-CH_2-O-R^2 \rightarrow HO-R^2 + R^1-C(=O)H$	Codeine Mescalin Papaverin Phenacetin
Oxidation of aromatic amines	$R-NH_2 \rightarrow R-NH-OH \rightarrow R-N=O$	Anilin derivatives

Biotransformation pathways of drugs, phase-I reactions

ليس كل الأدوية التي تدخل phase 1 تخرج highlipophilic وتدخل phase 2 وتفعل في phase 2

Phase II Reactions

- Metabolites from phase I **NOT** always hydrophilic or pharmacologically inactive.
- So, they enter phase II to produce conjugated products which have the following properties:

هو phase 2 هو صفات الدواء الذي يدخل

1. More polar.
2. More soluble in water.
3. Readily excretable.
4. Biologically inactive.
5. Non-toxic.
6. NON-metabolite

Phase II Reactions

- **Phase II includes:**
  1. Conjugation with glucuronic acid [Glucuronidation].
  2. Conjugation with sulphate. → NH, OH
  3. Conjugation with amino acids.
  4. Conjugation with glutathione.
  5. Acetylation.
  6. Methylation.

O, N, S, C — phase 2

*From high polar to less polar but the drug still polar.

1.Conjugation with glucuronic acid [Glucuronidation].

The major & most common route of conjugation reactions due to:

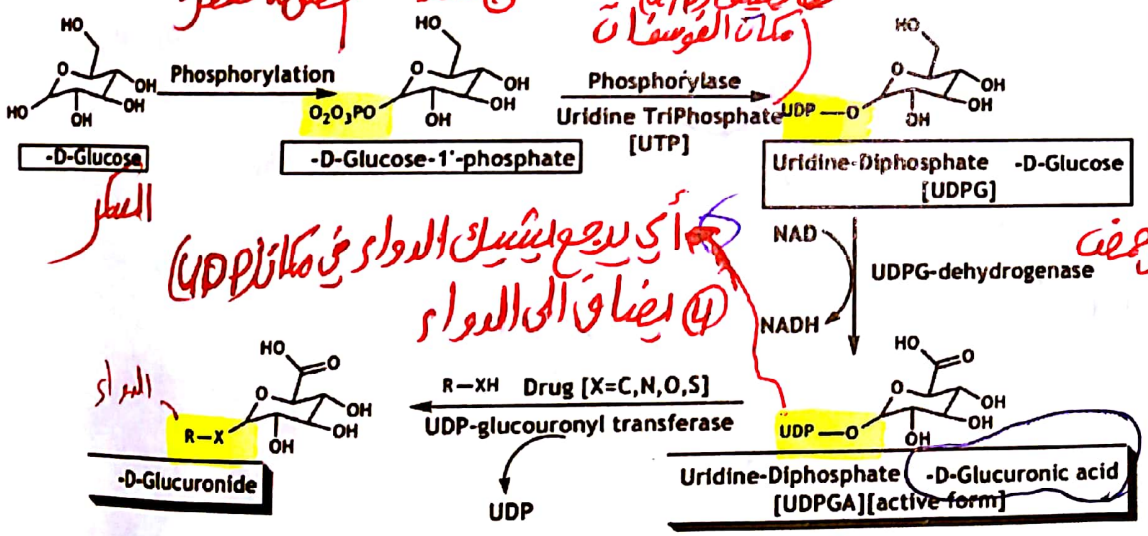
1. Glucuronic acid derived **from D-glucose** [**readily available** in body].
2. **Large number of functional groups** [phenols, alcohols, carboxylic acids & amines] → can combine enzymatically with glucuronic acid.
3. Formed glucuronides → **water soluble** → rapidly eliminated.

Mechanism of glucuronidation:[two steps]

Mechanism of glucuronidation:[two steps]

- Activation of glucuronic acid to **Uridine Diphosphate Glucuronic Acid** [**UDPGA**].
- Condensation of the drug [or phase I metabolite] with this active form.

The reaction is catalyzed by **UDP-glucuronosyl transferase enzyme**

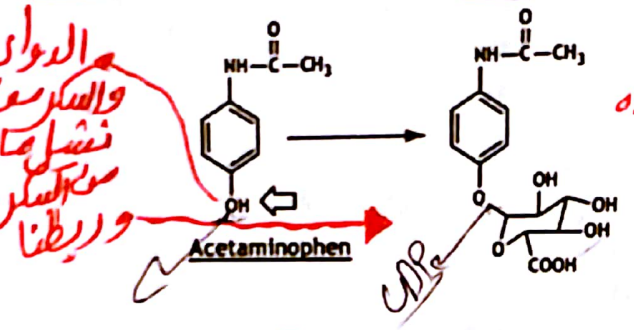


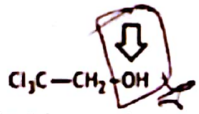
Glucuronidation NOT occur by D-glucuronic acid, it must be activated 1st to UDPGA'

Types of Glucuronides:

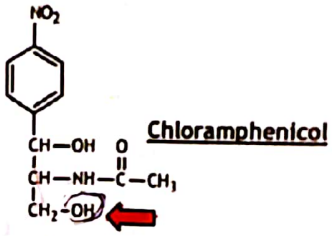
[I] O-Glucuronides

1. Ether glucuronides: [Alcohols, Phenols]



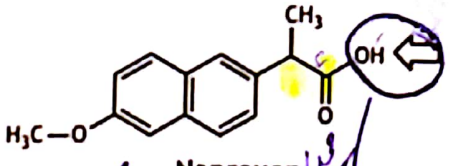


Trichloro ethanol
[metabolite of chloral hydrate]

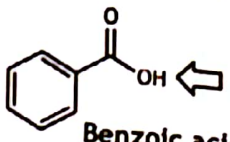


Chloramphenicol

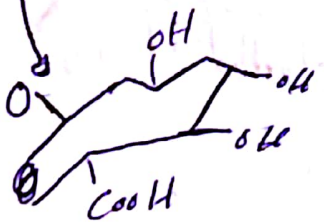
2. Acyl glucuronides [Aliphatic & aromatic carboxylic acids] → Esters



Naproxen



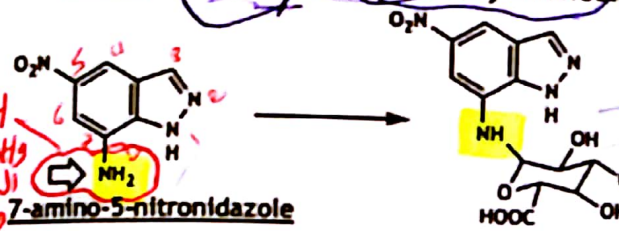
Benzoic acid

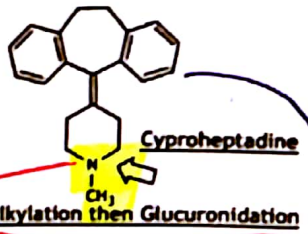


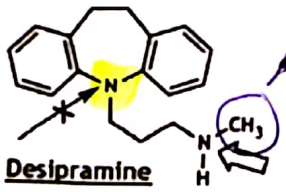
phase 2 إذا الدواء يحتوي N, O, S جاهز للاقتران مباشرة
لازم مثلا يكون عندك NH أو OH جاهز

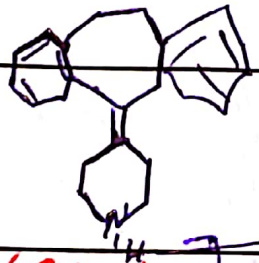
[ii] N-Glucuronides

- For aromatic amines, alkyl amines, amides, crabamates & non-aromatic nitrogenous heterocycles.
- Occur **ONLY** in primary and secondary amines. [3ry amine must be dealkylated 1st]



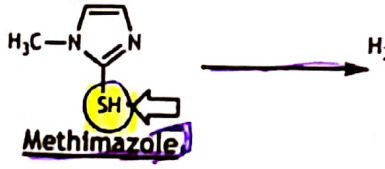


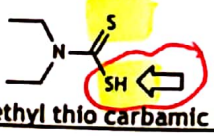


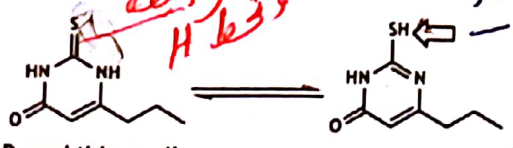


[iii] S-Glucuronides

For drug with thiol group [SH]



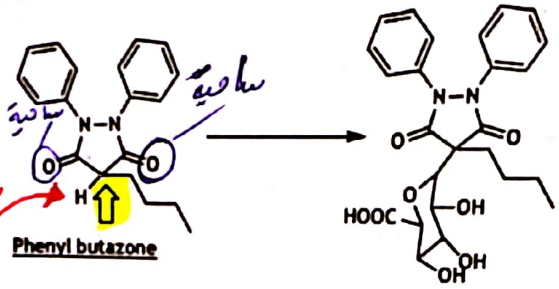




If disulfide [-S-S-] → (1) reduction 1st to make –SH → then (2) conjugation with glucuronic acid

[iv] C-Glucuronides

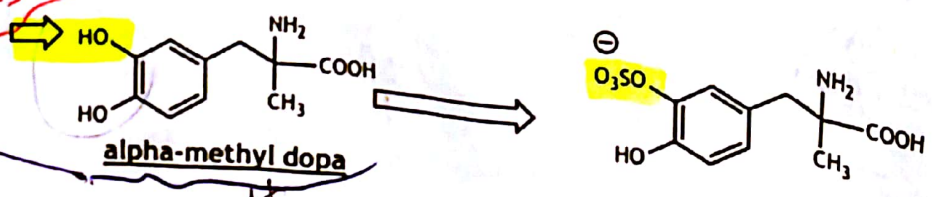
•Substances with 1,3-dicarbonyl structure → ↑ acidity of methylene C → C-glucuronide. [as **phenylbutazone**]



[2] Sulfate Conjugation

•**Mainly for drugs with –OH or –NH** [alcohols, phenols, aromatic amines & N-hydroxyls] → so, important reaction in metabolism of steroids, catecholamines, thyroxine & bile acids.

•Usually ↑ **water solubility** & drug excretion [**that pka of sulfonate group is 1-2**]

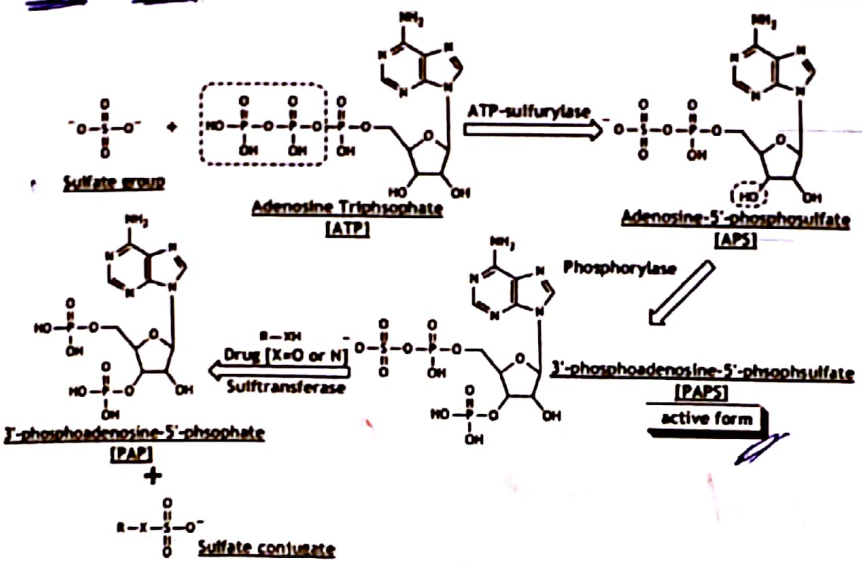


alpha-methyl dopa

Glucuronic acid مع Glucuronidation

Mechanism:[two steps]

- Inorganic sulfate must be activated 1st to 3-phospho adenosine-5'-phosphosulfate [PAPS].
- Transfer of sulfate to drug or drug metabolite [catalyzed by Sulfotransferase enzyme]

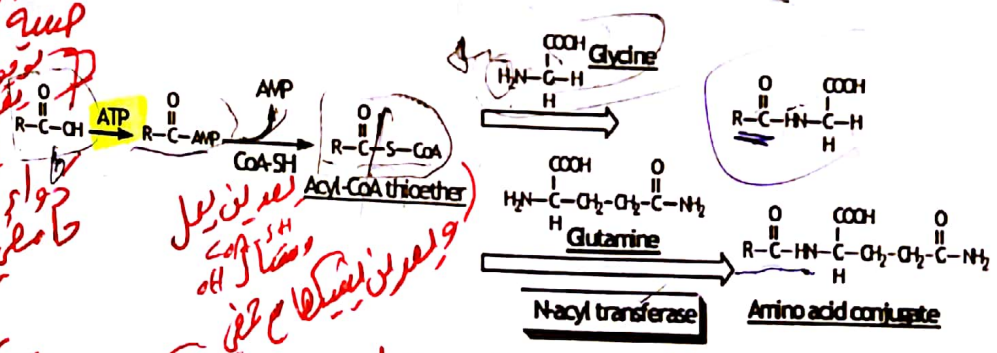


[3] Amino Acids Conjugation

- Most common amino acids used in conjugation are GLYCINE, GLUTAMINE.
- It needs activation of drug-COOH → as acyl Co-A [EXCEPTION]

Mechanism:[two steps]

- Activation of carboxylic acid group of drug substrate to highly reactive acyl-CoA.
- Transfer of activated drug to the amino acid, catalyzed b N-acyl transferse enzyme.



4] Glutathione or Mercapturic Acid Conjugation

- Important pathway for **DETOXIFICATION** of chemically reactive electrophilic compounds by nucleophilic SH group [that may cause protein & nucleic acids damage].
- GSH is **tripeptide**: [γ-glutamyl cysteinyl glycine] found in most tissues

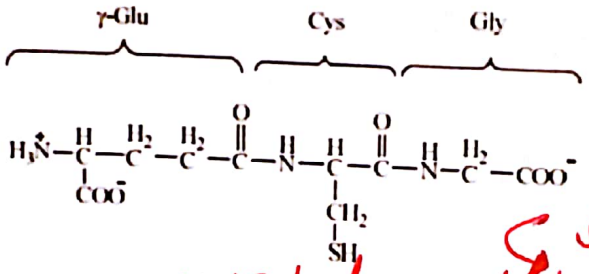
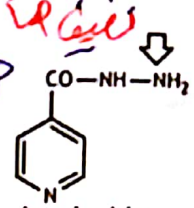
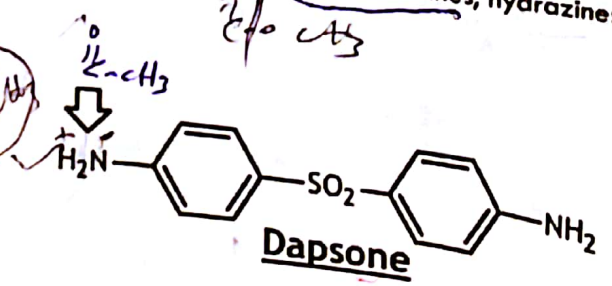


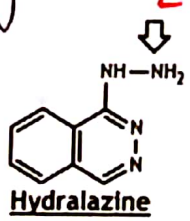
Figure 59: the structure of glutathione

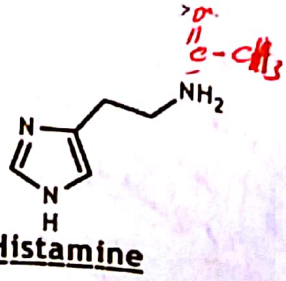
⑤ Acetylation

- Very important pathway for drugs with **1ry amino group** [aromatic amines, hydrazines, hydrazides, aliphatic amines]



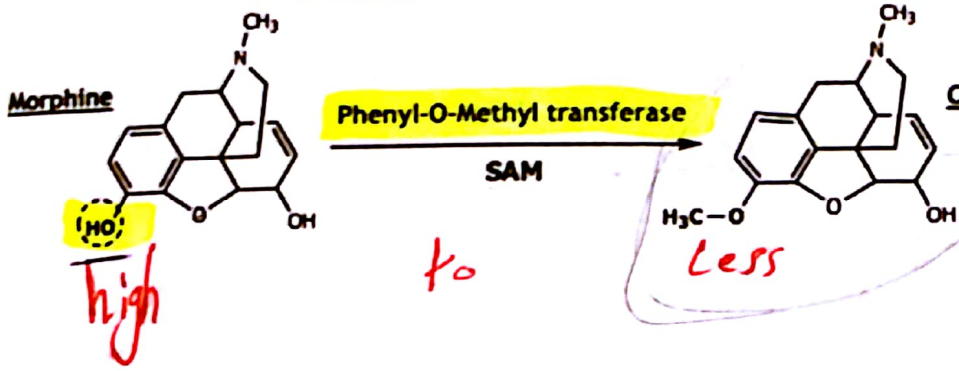






⑥ Methylation – from high to less

- Minor pathway in drugs metabolism, but very important in biosynthesis & metabolism of endogenous substances (Catecholamines).
- Occur for compounds with OH group



weaker and less toxic than morphine

Factors affect drug metabolism:

[1] Age:

- Deficiency of microsomal enzymes in newborn child → prolongation of action & diverse reactions of some drugs. E.g. Chloramphenicol.

[2] Sex differences:

Rate of metabolism of some drugs are faster in male > females. E.g. Diazepam

[3] Physiologic or disease state:

- Diseases alter liver function → affect metabolism rate.

[4] Genetic factors:

- Absence of special gene responsible for synthesis of enzymes essential in normal metabolism → metabolic disorders [affect intensity & duration of the drug].

. biliary كان الدواء high lipophilic ضيف له سكر ويخرج بواسطة
less يخرج مع البول

[5] Inhibition of drug metabolism:

•Inhibition of enzymes responsible for metabolism of a drug → prolongation of its duration → toxicity.

E.g. **Cimetidine** inhibit Cyp-450 enzyme

[6] Induction of drug metabolism:

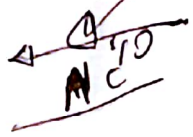
•Induction of enzymes responsible for metabolism of a drug → ↓ duration → needed to be taken in **higher doses.**

•E.g. **Phenobarbitone** & **Alcohols** → ↑ level of Cyp-450 (chronic alcoholists need higher doses of sedatives).

[7] Chemical structure & Stereoisomerism:

•**Procaine** & **Procainamide** → differ in their metabolism.

(-)Hexobarbitone & **(-)Warfarin** → metabolized **faster** than their (+) isomers



[8] Species & Strain differences:

•**Amphetamine** → metabolized by either oxidative deamination or aromatic hydroxylation.

•**In man** → oxidative deamination is major **While in rats** → aromatic hydroxylation is major.

Metabolic Stabilization

- Achieved by replacing a *labile group* with another, less or non-reactive moiety, provided this change is not detrimental to PD activity.

Yielding unmetabolized drugs

Metabolic Stabilization cont..

This could be achieved by:

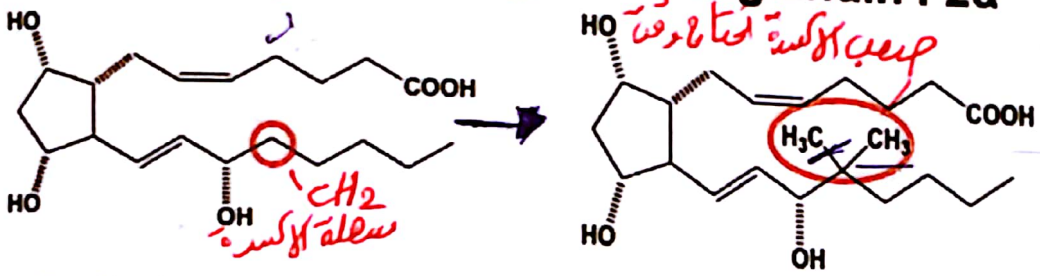
1. Replacement of a $-CH_2-$ group with a $-CF_2-$ group
2. Introduction of an *N-tert*-butyl group to prevent N-dealkylation
3. Inactivation of aromatic rings towards oxidation by substituting them with strongly electron-withdrawing groups (e.g., CF_3, SO_2NH_2, SO_3^-)
4. Replacement of a labile ester linkage with an amide group
5. Protection of the labile moiety by steric shielding

① اذا كان معلق مركبة CH_2 أستبدلها بـ $C(CH_3)_2$ او CF_2

Metabolic Stabilization cont..

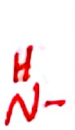
- Replacement of a $-CH_2-$ group with a $-C(CH_3)_2-$ or a $-CF_2-$ group

Prostaglandin F2α → **16,16 dimethyl Prostaglandin F2α**



The dimethyl subsituent blocks the inactivation of the prostaglandins by blocking the oxidation of alc. OH to the Ketone, and so has longer half-life in man.

② اذا معلق NH هنا لاتشيل كبيرها خليها عدوية خليها صعب حل الكبيرة تشيلها

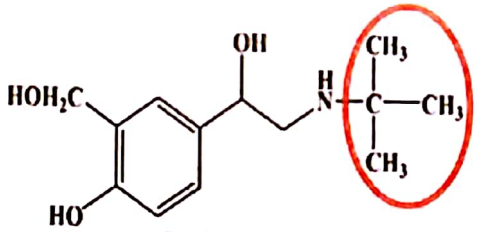


خليها bulky

Metabolic Stabilization cont..

- Introduction of an N-tert-butyl group to prevent N-dealkylation

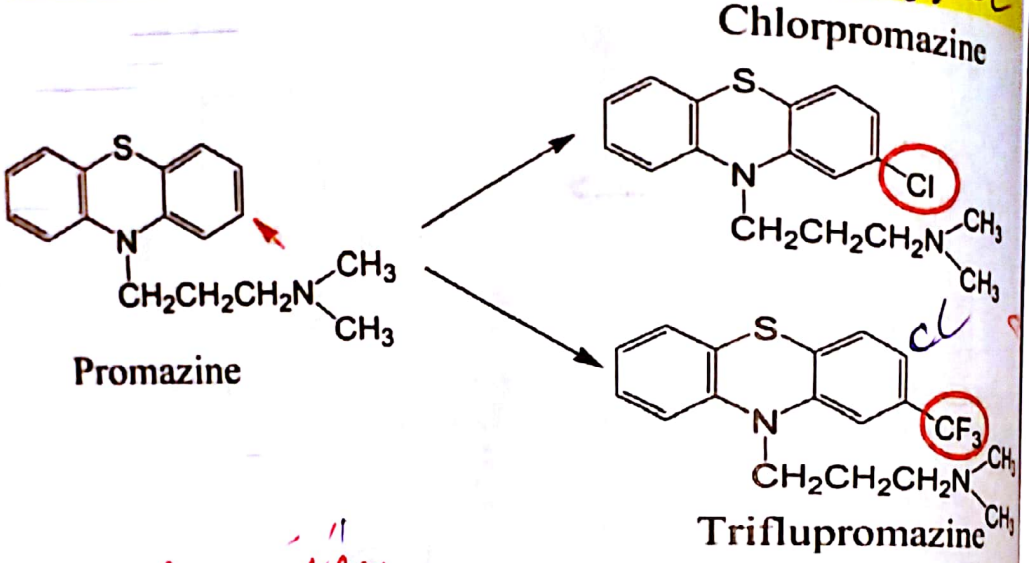
(N-tert) N-C(CH3)3 خليها ← يدل ماكانت N



Salbutamol

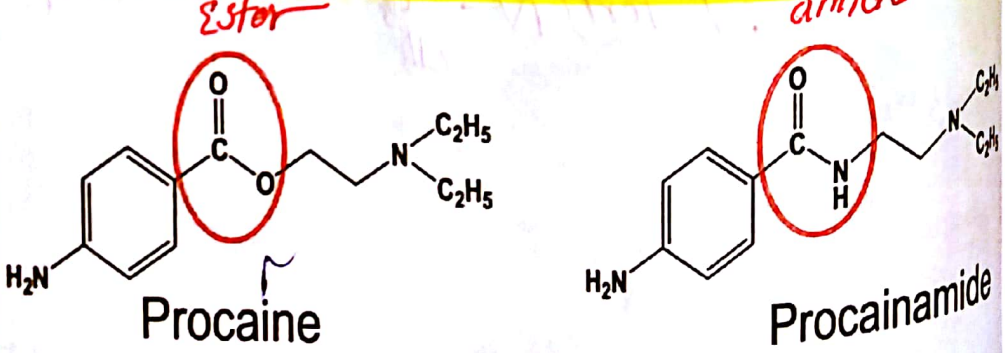
Metabolic Stabilization cont..

- Inactivation of aromatic rings towards oxidation by substituting them with strongly electron-withdrawing groups (e.g., CF_3, SO_2NH_2, SO_3^-)

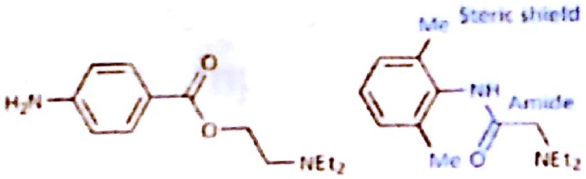


Metabolic Stabilization cont..

- Replacement of a labile ester linkage with an amide group

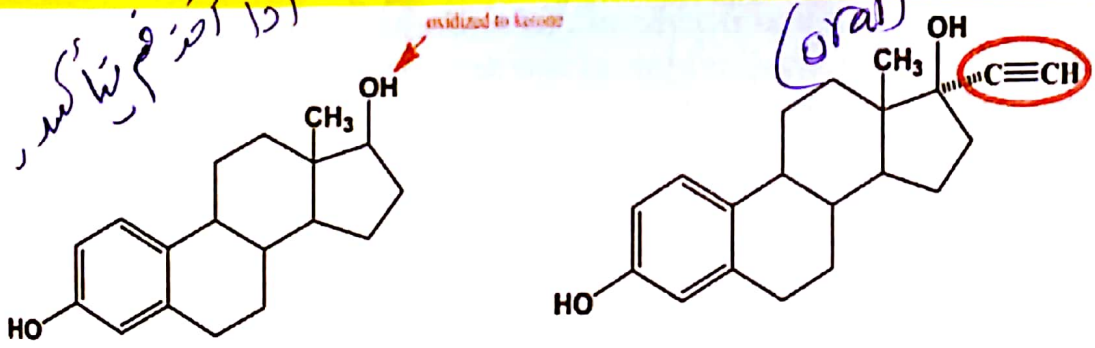


For example procaine is a good local anaesthetic, but it is short-lasting because its ester group is quickly hydrolyzed.
Changing the ester group to the less reactive amide group reduces chemical hydrolysis.
Furthermore, the presence of two -methyl groups on the aromatic ring helps to shield the carbonyl group from attack by nucleophiles or enzymes.
This results in the longer acting, local anesthetic lidocaine.



Metabolic Stabilization cont..

- Protection of the labile moiety by steric shielding



The ethinyl group blocked the oxidation of the 17β- hydroxy group to ketone

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Metabolic Stabilization cont..

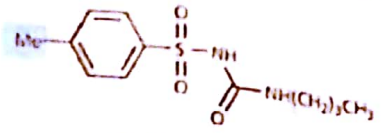
ADVANTAGES

- Longer half-lifes
- Decreased possibilities of drug interactions
- Decreased inter- and intra-patient variability
- Decreased species differences
- Decreased number and significance of active metabolites

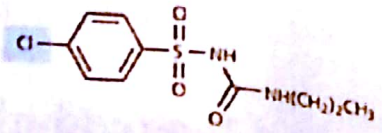
Metabolic blockers

On the same lines, a popular method of protecting aromatic rings from metabolism at the para-position is to introduce a fluoro substituent. For example, CGP

an anticancer agent and was found to undergo oxidative metabolism at the para-position of the aromatic rings. Fluoro-substituents were successfully added to block this metabolism and the analogue CGP 53353 was also put forward for clinical trials.



Tolbutamide



Chlorpropamide